Office Action Summary	Application No. 08/973,021	Applicant(s) sen, Mouritsen, Hindersson, Duch, Sorensen, Dal
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Apr 24, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-18, 20-26, 30, 31, 37-42, 48, 53, and 59-70* is/are pending in the application.

Of the above, claim(s) ______ is/are withdrawn from consideration.

☐ Claim(s) ______ is/are allowed.

☒ Claim(s) *1-18, 20-26, 30, 31, 37-42, 48, 53, and 59-70* is/are rejected.

☐ Claim(s) ______ is/are objected to.

☐ Claims ______ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on ______ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on ______ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) ______.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: ______.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). ______

☒ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Supplemental Office Action

1. This office action is supplemental to the office action mailed on April 7, 2000, due to errors in the rejection of claims 1-18, 20-26, 30 ,31, 37-42, 48, 53 and 59-70 under 35 U.S.C. 103(a). The mailing date of this supplemental office action will restart the time period for response.

Response to Arguments

2. Applicant's arguments with respect to claims 1-18, 20-26, 30, 31, 37-42, 48, 53 and 59-70 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-18, 20-26, 30, 31, 37-42, 48, 53 and 59-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claims 1, 42, 69 and 70 recite in step "d)", "wherein the pool of appropriate vectors in step (a) contains synthetic totally random DNA sequences". It is not clear from this language whether each vector contains the synthetic totally random DNA sequences or if they may be present in some subset of the set of vectors being claimed. As such the claim is vague and indefinite.

6. Claims 1, 42, 69 and 70 recite in step "d)", "wherein the pool of appropriate vectors in step (a) contains synthetic totally random DNA sequences". It is not clear from this language how the totally synthetic DNA is associated with the vectors. Does the pool contain synthetic totally random DNA sequences in addition to the vectors, or is the synthetic totally random DNA sequences incorporated into the vector sequences? This language is unclear and therefore vague and indefinite.

7. Claims 1, 42, 69 and 70 recite in step "(e)" and again in step "(f)", "the sequences of ribonucleic acids or peptides **effecting** alteration of the preselected cellular function". It is not clear from the claim that the sequences are causing any effect. There is an associative link between the presence of the vectors in the cells and the claimed alteration of the preselected cellular function, but there is no causative link between the sequences of ribonucleic acids or peptides expressed by the vectors in the cell and the altered preselected cellular function. Therefore the language of the phrase "the sequences of ribonucleic acids or peptides **effecting** alteration of the preselected cellular function" is unclear, and as such is vague and indefinite.

8. Claims 1, 42, 69 and 70 at the junction of steps "(e)" and "(f)" recites "and/or". This raises the condition of ignoring all of the previous steps "(a)" through "(e)" and leaving just step "(f)" as a limitation of the claim. It is also arguable that the "and/or" term here may refer back to just step "(a)" or "(b)" or "(c)" or "(d)" or "(e)" or a combination of the some or all of the previous steps. As such, the claim is vague and indefinite.

9. Claims 1, 42, 69 and 70 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting an essential step, such omission does not set forth the method in clear and unambiguous terms. See MPEP § 2172.01. The omitted step is a correlation, or recapitulation step at the end of the claim which restates the preamble.

10. Claims 3-5, 8, 9, 11, 14, 15, 22, 30, 31, 38 and 59-68 recites the limitation "synthetic random DNA". There is insufficient antecedent basis for this limitation in the claim. Changing the phrase to "synthetic totally random DNA" would cure the deficiency.

11. Claim 7 recites the limitation "ligation of DNA fragment into a vector is optimized" in line 2. There is insufficient antecedent basis for this limitation in the claim.

12. Claim 8 recites the limitation "the number of eukaryotic cells" in line 3. There is insufficient antecedent basis for this limitation in the claim.

13. Claim 15 contains the trademark name "PCR". Use of trademarks in the claims is specifically prohibited. Trademarks are not specific identifiers of a chemical or compound, or in this case a method, and as such are vague and indefinite. Correction is required.

14. Claim 15 recites the limitation "the viral DNA" in line 2. There is insufficient antecedent basis for this limitation in the claim.

15. Claim 15 recites "viral DNA introduced into the cells is amplified directly by PCR and followed by retransfection of further cells". This phrase is unclear, since the cells which were originally transfected with the viral DNA are already transfected with the viral DNA and it is not clear how the "retransfection" of the cells would make any difference in the method. Also, the term "further cells" is unclear as to its meaning. Either the step is redundant and should be deleted, or the claim should be rewritten to more clearly identify the desired step.

16. Claim 16 recites the limitation "the viral titer of retroviral packaging cell lines" in line 2. There is insufficient antecedent basis for this limitation in the claim.

17. Claim 17 recites a method of "transfecting a packaging cell line constructed from a vector". It is not clear how a cell line is constructed from a vector. This language is inconsistent with normal usage and as such is vague and indefinite.

18. Claim 17 adds a step to claim 9 including a packaging cell line, but does not relate the added step to any part of the method. As such , the method is missing steps to explain the connection of said added step to the method steps of claim 9.

19. Claim 18 adds a step to claim 9 including a semi-packaging cell line, but does not relate the added step to any part of the method. As such , the method is missing steps to explain the connection of said added step to the method steps of claim 9.

20. Claim 18 recites "a cell line with a corresponding minivirus/vector". It is unclear how the "cell line with a corresponding minivirus/vector" relates to the claimed method of claim 9. Claim 18 is missing steps which would clarify the relationship of "a cell line with a corresponding minivirus/vector" to the viruses and cell line of claim 9.

21. Claims 20 and 41 recite that the sequences of ribonucleic acids or peptides **effecting** alteration of the preselected cellular function. It is not clear from the claim that the sequences are causing any effect. There is an associative link between the presence of the vectors in the cells and the claimed alteration of the preselected cellular function, but there is no causative link between the sequences of ribonucleic acids or peptides expressed by the vectors in the cell and the altered preselected cellular function. Therefore the language of the phrase "ribonucleic acids or peptides **effecting** alteration" is unclear, and as such is vague and indefinite.

22. Claim 21 recites the limitation "expressed random peptides" in lines 4 and 6. There is insufficient antecedent basis for this limitation in the claim.

23. Claim 21 recites the limitation "expressed peptides" in line 4. There is insufficient antecedent basis for this limitation in the claim.

24. Claim 21 recites the limitation "random peptide sequences" in lines 5 and 7. There is insufficient antecedent basis for this limitation in the claim.

25. Regarding claim 23, the phrase "(for example) e.g." renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

26. Claim 25 depends from claim 1. Claim 25 recites the "screening"of a cell surface protein or receptor. Claim 1 recites "said screening being one which does not require knowledge of 1) chains of mechanisms in the cell, 2) enzymes in the cell, 3) signaling pathways in the cell, or 4) receptors in the cell which generate the preselected cellular function". Claim 1 restricts the prior knowledge of the receptors making the limitation of claim 25 impossible.

27. Claim 26 depends from claim 1. Claim 26 recites the "preselected cellular function"is a cell surface protein. Claim 1 recites "said screening being one which does not require knowledge of 1) chains of mechanisms in the cell, 2) enzymes in the cell, 3) signaling pathways in the cell, or 4) receptors in the cell which generate the preselected cellular function". Claim 1 restricts the prior knowledge of the preselected cellular function making the limitation of claim 26 impossible.

28. Claim 41 recites the limitation "effecting alteration" in 2. There is insufficient antecedent basis for this limitation in the claim.

29. Claim 42 recites the limitation "peptides effecting up-regulation" in section (e)", line 2. There is insufficient antecedent basis for this limitation in the claim.

30. Claims 61 and 66 recite the limitation "enable" in line 2. There is insufficient antecedent basis for this limitation in the claim. Replacing "enable" with "encode" would cure the deficiency.

Claim Rejections - 35 USC § 103

31. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

32. Claims 1-18, 20-26, 30 ,31, 37-42, 48, 53 and 59-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/04824 et al. (of record) in view of, LaBean et al., Dube et al., WO 94/29469, US Pat No. 5,935,823, Karttunen et al. and Von Melchner et al.

WO 95/04824 taught (see especially the abstract and pages 2, 3, 7, example 6 and example 13) a method of transducing eukaryotic cells with a viral vector which stably integrated into the genome of the cell at one to a few copies per cell, expressing an encoded sequence, which may be totally random sequence, identification of an expressed trait in the cell, selecting said cell, and recovering the DNA sequence encoded by the viral vector. The encoded sequence may then be amplified and sequenced. Packaging cells may be employed to prepare the viral vector for infection of the host cell where the packaging vector may contain gag. The encoded sequence may be fused with or inserted into a sequence which encodes for a protein. The eukaryotic cells may be hematopoietic cells, and the DNA encoded products may be hematopoietic cell receptors.

WO 95/04924 did not teach that the DNA inserts were short sequences which were not genes. Also not taught was a retroviral packaging system with a gag, pol and env sequence

WO 95/04924 did not teach that the DNA inserts were short sequences which were not genes. Also not taught was a retroviral packaging system with a gag, pol and env sequence provided from the packaging cell line. WO 95/04824 did not teach the random codon synthesis, nor the CMV promoter, nor the identification of T-cell epitopes.

LaBean et al. taught (see the entire article) the method of generating random sequences encoding random amino acids, and discussed the advantages of introducing random codons, as well as partially random sequences which reduce or eliminate stop codons in the encoded sequence.

Dube et al. taught (see the entire article) the method of using totally or partially random sequences in a viral vector to transform a eukaryotic cell. The transformed cell was screened for biologically active DNA sequences to identify nucleic acid sequences which encoded unique functions. The encoded DNA was isolated and sequenced, and the encoded RNA and peptides were also sequenced and identified.

US Pat No. 5,935,823 taught (see especially the abstract and the summary and column 21) the method of using viral vectors containing totally random sequences to transform a eukaryotic cell to identify nucleic acid sequences which encoded unique functions. The random sequences of DNA was isolated and sequenced, and the encoded RNA and peptides were also sequenced and identified.

WO 94/29469 taught (see especially page 10, lines 30-32) the equivalence of promoters such as CMV promoters to other well known eukaryotic promoters, such as the viral LTR promoters taught in WO 95/04824.

Karttunen et al. taught (see especially the abstract, introduction and discussion) the well known cloning and identification of T-cell epitopes.

Von Melchner et al. taught (see especially the abstract and the figures) the well known and advantageous use of packaging cells for the production of retroviral vectors which contain the gag, pol and env genes which vectors are to be used in identifying and characterizing encoded foreign genes contained in the viral vectors.

It would have been obvious to one of ordinary skill in the art at the time of filing the instant application to combine the method of transducing eukaryotic cells with a viral vector which stably integrated into the genome of the cell at one to a few copies per cell, expressing an encoded sequence, which may be totally random sequence, identification of an expressed trait in the cell, selecting said cell, and recovering the DNA sequence encoded by the viral vector. The encoded sequence may then be amplified and sequenced. Packaging cells may be employed to prepare the viral vector for infection of the host cell. The encoded sequence may be fused with or inserted into a sequence which encodes for a protein of WO 95/04824 with the method of generating random sequences encoding random amino acids, and discussed the advantages of introducing random codons, as well as partially random sequences which reduce or eliminate stop codons in the encoded sequence of LaBean et al., and the method of using totally or partially

random sequences in a viral vector to transform a eukaryotic cell where the transformed cell was screened for biologically active DNA sequences to identify nucleic acid sequences which encoded unique functions and the encoded DNA was isolated and sequenced, and the encoded RNA and peptides were also sequenced and identified of Dube et al., and the method of using viral vectors containing totally random sequences to transform a eukaryotic cell to identify nucleic acid sequences which encoded unique functions and the encoded DNA was isolated and sequenced, and the encoded RNA and peptides were also sequenced and identified of US Pat No. 5,935,823, and where WO 94/29469, Karttunen et al. and Von Melchner et al. each taught well known adaptations of the methods of eukaryotic transformation and expression for the purpose of identifying the expressed sequences and their respective expressed proteins and peptides because the methods of WO 95/04824 et al., LaBean et al., Dube et al. and WO 94/29469 were each directed to the expression of DNA sequences to identify the expressed sequences and their respective proteins and peptides. The methods of each of WO 95/04824 et al., LaBean et al., Dube et al. and WO 94/29469 taught well known and useful methods of discovery of sequences of DNA and their transcripts and expressed protein and peptide sequences.

One of ordinary skill in the art would have been motivated at the time of filing the instant application to combine the method of transducing eukaryotic cells with a viral vector which stably integrated into the genome of the cell at one to a few copies per cell, expressing an encoded sequence, which may be totally random sequence, identification of an expressed trait in the cell, selecting said cell, and recovering the DNA sequence encoded by the viral vector. The

encoded sequence may then be amplified and sequenced. Packaging cells may be employed to prepare the viral vector for infection of the host cell. The encoded sequence may be fused with or inserted into a sequence which encodes for a protein of WO 95/04824 with the method of generating random sequences encoding random amino acids, and discussed the advantages of introducing random codons, as well as partially random sequences which reduce or eliminate stop codons in the encoded sequence of LaBean et al., and the method of using totally or partially random sequences in a viral vector to transform a eukaryotic cell where the transformed cell was screened for biologically active DNA sequences to identify nucleic acid sequences which encoded unique functions and the encoded DNA was isolated and sequenced, and the encoded RNA and peptides were also sequenced and identified of Dube et al., and the method of using viral vectors containing totally random sequences to transform a eukaryotic cell to identify nucleic acid sequences which encoded unique functions where the encoded DNA was isolated and sequenced, and the encoded RNA and peptides were also sequenced and identified of US Pat No. 5,935,823, and where WO 94/29469, Karttunen et al. and Von Melchner et al. each taught well known adaptations of the methods of eukaryotic transformation and expression for the purpose of identifying the expressed sequences and their respective expressed proteins and peptides because WO 95/04824 taught the use of retroviral vectors containing DNA sequences which may be totally random sequence to transform eukaryotic cells at a low copy number (which may be one copy) per cell to rapidly and efficiently identify sequences which were expressed in the cells, where the sequences expressed RNA and protein or peptides which were

recognized by some trait or characteristic, which cells may be hematopoietic cells and the vector DNA may express a hematopoietic cell receptor. LaBean et al. states at the abstract "[l]ibraries of random sequence polypeptides are useful as source of unevolved proteins, novel ligands, and potential lead compounds for the development of vaccines and therapeutics. The expression of small random peptides has been achieved previously using DNA synthesized with equimolar mixtures of nucleotides...Semirandom DNA, synthesized with a designed, three-residue repeat pattern, can encode libraries of very high diversity and represents an important tool for the construction of random polypeptide libraries." providing excellent motivation to produce random codon synthetic DNA inserts in the vectors of WO 95/04824. Dube et al. at the abstract recites "[s]electing biologically active DNA sequences from large random populations provides a new method for identifying nt [nucleotide] sequences with unique functions." Dube et al. concludes at page 46, column 1, bottom "[i]t seems a reasonable expectation that this method, combined with other methods, collectively referred to as 'applied molecular evolution' will lead to the production of new enzymes and other biological molecules that are entirely different from those present in nature." US Pat No. 5,935,823 taught at column 11, line 49-50, "[]the present invention relates to novel reagents and the process for making them. The invention provides a process for synthesizing and identifying new binding reagents of specific affinity", which is followed at lines 57-58 "[t]he polypeptides or proteins are expressed in prokaryotic or eukaryotic cells as hybrid fusion proteins...", and at column 12, line 66, bridging to the top of column 13 "the first sequence comprises a group of sequences generated by random synthesis....to form a

library of vectors expressing fusion proteins...". Karttunen et al. merely provide an exemplary method of producing hematopoietic cell receptors, which are T-cell receptors, which are T-cell epitopes, which are MHC molecules. WO 94/29469 provides well known teachings on the equivalence of eukaryotic promoters such as CMV and LTR, while Von Melchner provides teachings on the well known packaging of retroviral vectors which may include gag, pol and env proteins to facilitate transduction of target cells. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of WO 95/04824 et al. with LaBean et al., Dube et al., WO 94/29469, US Pat No. 5,935,823, Karttunen et al. and Von Melchner et al.

Conclusion

33. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
April 24, 2000

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